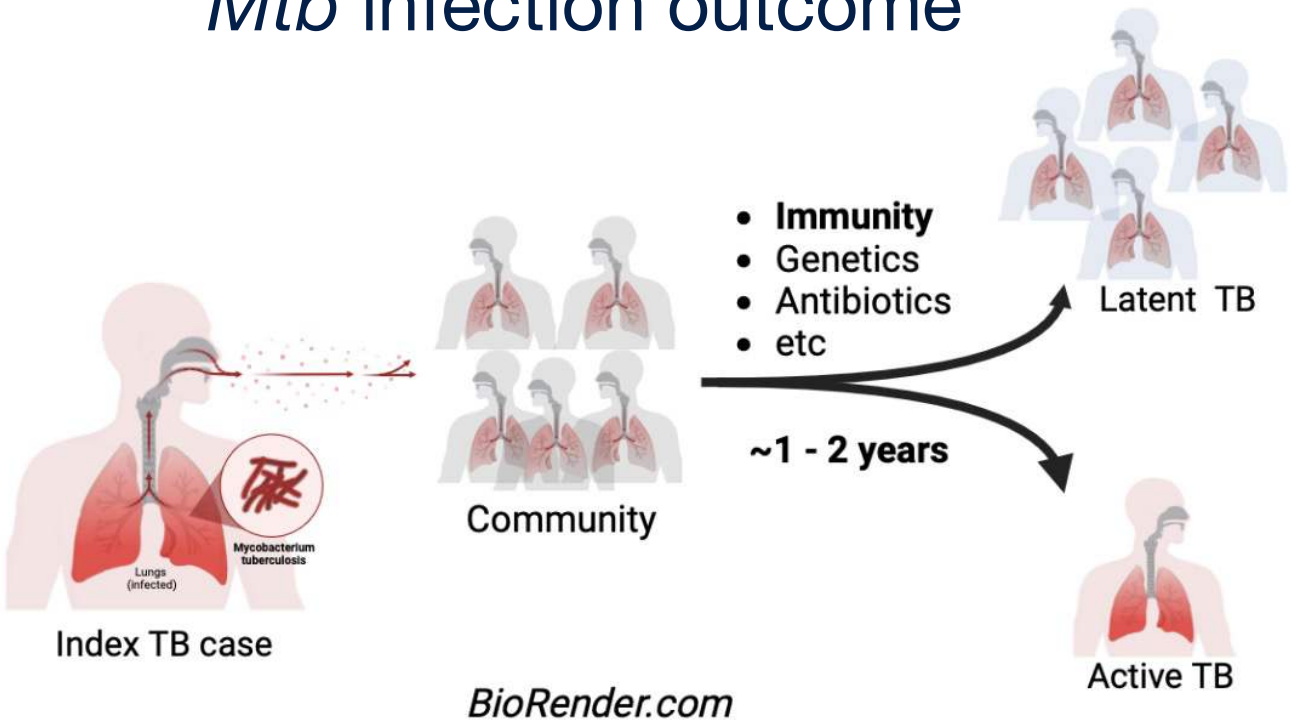
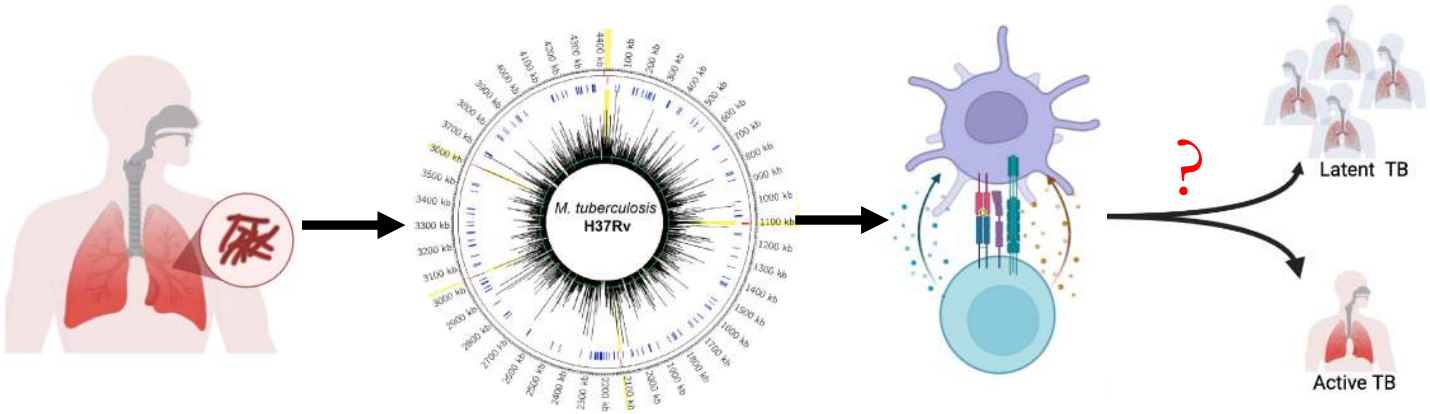
Is there evidence for disease-specific antigens?

Paul Ogongo, PhD

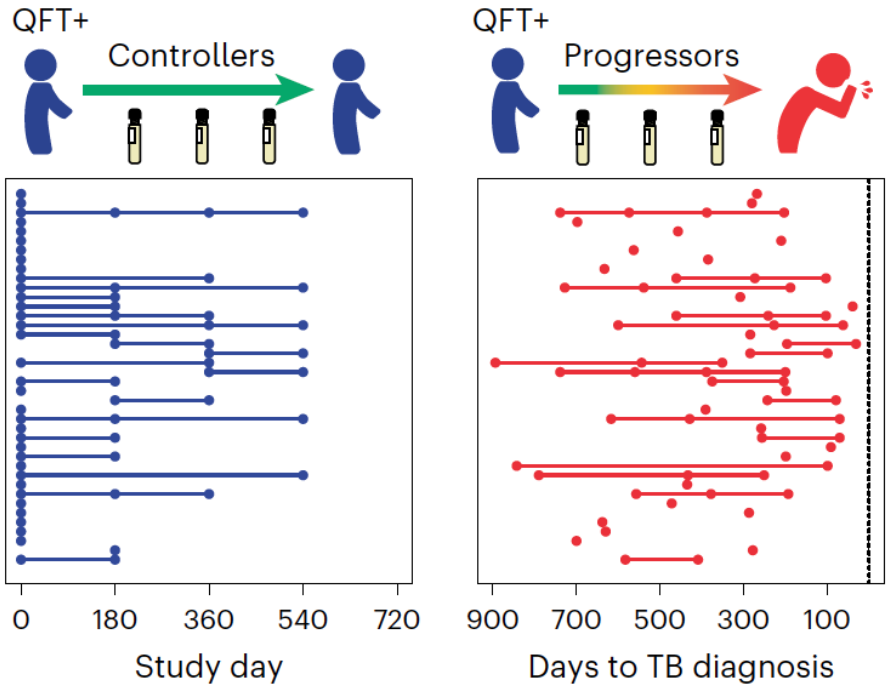
Helen Hay Whitney Foundation Fellow,
Postdoctoral Scholar,
Joel Ernst Lab,
University of California San Francisco

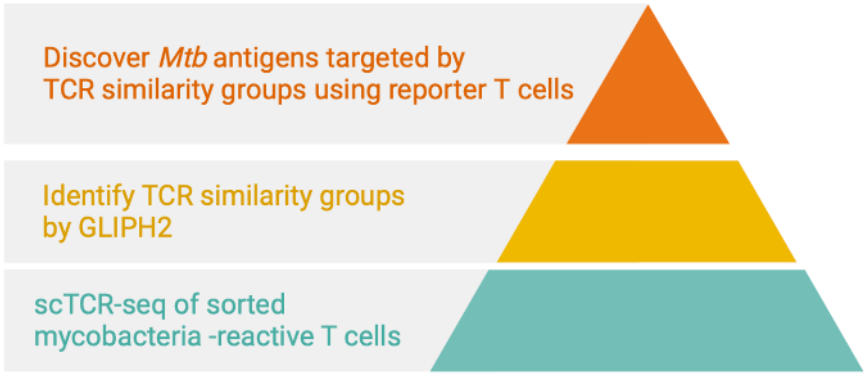
Mtb infection outcome





Distinct *Mtb* antigens are associated with infection outcomes





- Longitudinal cohorts (ACS and GC6-74 cohorts)
  Well-characterized with definite clinical outcomes
- Computational/Systems biology

Munyaradzi M et al 2023

Distinct *Mtb* antigens are associated with infection outcomes

Cluster	Clone ID	CDR3α	TRAV	TRAJ	CDR3β	TRBV	TRBJ	HLA-a	HLA-b	Epitope	Protein	Association
SVAL	ACS024	CAGTNTGNQFYF	27	49	CASSVALQGVHTQYF	9	2-3	DRA*01:01	DRB1*15:03	MHVSFVMAYPEMLAA	Rv1195(PE13)	Controller
	ACS025	CAGPTGGSYIPTF	25	6	CASSVALATGEQYF	9	2-7	DRA*01:01	DRB1*15:03	MHVSFVMAYPEMLAA	Rv1195(PE13)	Controller
GEAK	ACS088	CAVRDPGNTDKLIF	1-2	34	CSARASGGEAKNIQYF	20-1	2-4	DRA*01:01	DRB5*01:01	AAVVRFQEAANKQKQ	Rv3874(CFP10)	Controller
S%EDRGNTE	ACS060	CAVPNSGYSTLTF	21	11	CAISQEDRGNTEAFF	10-3	1-1	DRA*01:01	DRB3*01:01	MSRAFIIDPTISAID	Rv3616c(EspA)	Progressor
	ACS061	CAAPNSGYSTLTF	21	11	CAISGEDRGNTEAFF	10-3	1-1	DRA*01:01	DRB3*01:01	MSRAFIIDPTISAID	Rv3616c(EspA)	Progressor
S%LAAGQET	ACS254	CATPNQAGTALIF	1-2	5	CASSILAAGQETQYF	19	2-5	DRA*01:01	DRB1*04:01	-	Mtb lysate	Progressor
	ACS255	CAVMNQAGTALIF	1-2	5	CASSLLAAGQETQYF	11-1	2-5	DRA*01:01	DRB1*04:01	-	Mtb lysate	Progressor
	ACS256	CAAPNQAGTALIF	1-2	5	CAWSVLAAGQETQYF	30	2-5	DRA*01:01	DRB1*04:01	-	Mtb lysate	Progressor

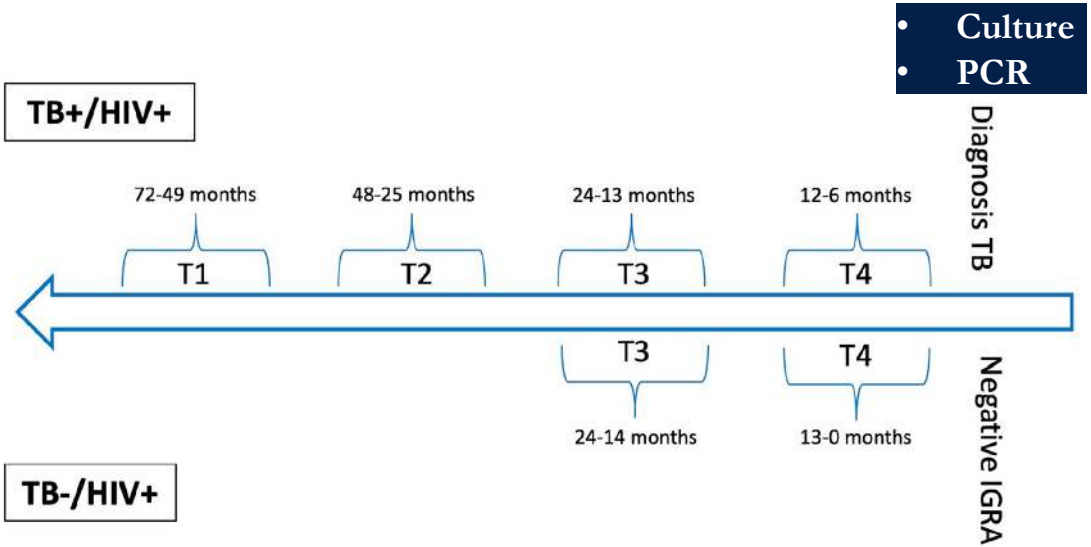
Do these antigens induce different immune responses?

If so, at what point do the responses diverge into controller vs progressor groups?

Munyaradzi M et al 2023

Distinct *Mtb* antigen immune responses precede development of confirmed TB disease

Swiss HIV Cohort
Matched by
age, sex, BMI,
CD4 cell count,
HIV viral load.



Novel *Mtb* antigens
(Rv0081, Rv1733c, Rv2031c, Rv0867c, Rv2389c, Rv3407, Rv2346/47c, Rv2431c, Rv3614/15c, and Rv3865)

Cytokines in cell supernatants
GM-CSF, IFN-γ, IP-10, IL-1RA, IL-6, TNF-α

Meier NR et al 2021

Distinct *Mtb* antigen immune responses precede development of confirmed TB disease

TABLE 2 | Discriminatory potential of antigen-cytokine in cases and controls at T3 and T4.

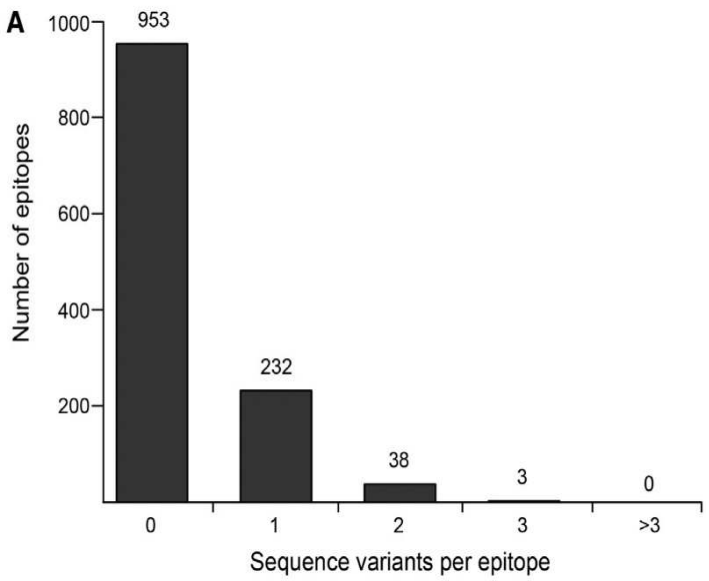
Antigen	Cytokine	TP	TB	*n*	Controls	*n*	*p*-value	AUROC	Cut-off	Sensitivity (%)	Specificity (%)
Rv2431c	IP-10	T4	6.0 (1.2–159.8)	8	−9.2 (−6.8-3.2)	7	<0.004	0.929 (95% CI = 0.800–1)	2.2	0.87	1
Rv3614/15c	IP-10	T4	8.6 (0.6–238.8)	8	−0.7 (−9.3-4.7)	7	<0.002	0.964 (95% CI = 0.881–1)	5.4	0.87	1
Rv2031c	TNF-α	T4	304.1 (57.3-2381.0)	8	9.2 (-72.9-103.1)	8	< 0.002	0.953 (95% CI= 0.862-1)	72.9	0.87	1
Rv2346/47c	TNF-α	T4	115.5 (6.6–1004.0)	8	−38.4 (-389.9-96.6)	8	<0.002	0.937 (95% CI = 0.824–1)	25.3	0.87	1
Rv2031c	TNF-α	T3	185.6 (46.5–1390.6)	7	2.6 (−814.1-447.7)	9	<0.004	0.921 (95% CI = 0.76–1)	36.3	1.0	0.89

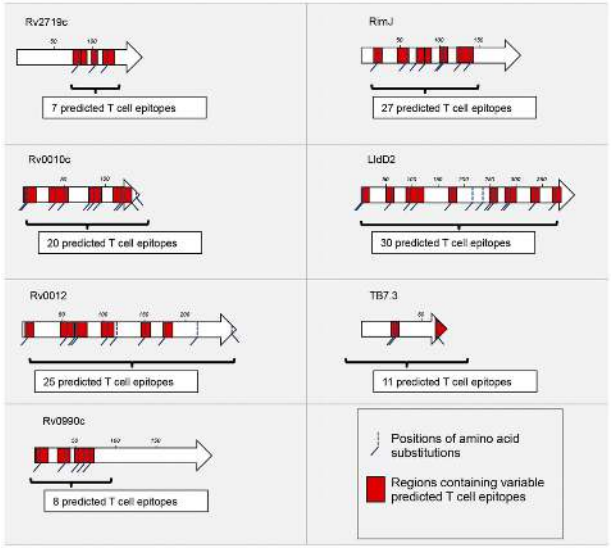
Median concentrations of cytokines (pg/ml) and ranges (in parenthesis) induced by stimulation of lymphocytes overnight and ability to discriminate between TB group and control group. AUROC, Area under the receiver operating characteristics.

Dominant TNF-α has previously been shown to discriminate LTBI from ATB Harari et al 2011

Meier NR et al 2021

Distinct *Mtb* antigens determine CD4 T cell differentiation





Coscolla M et al 2015

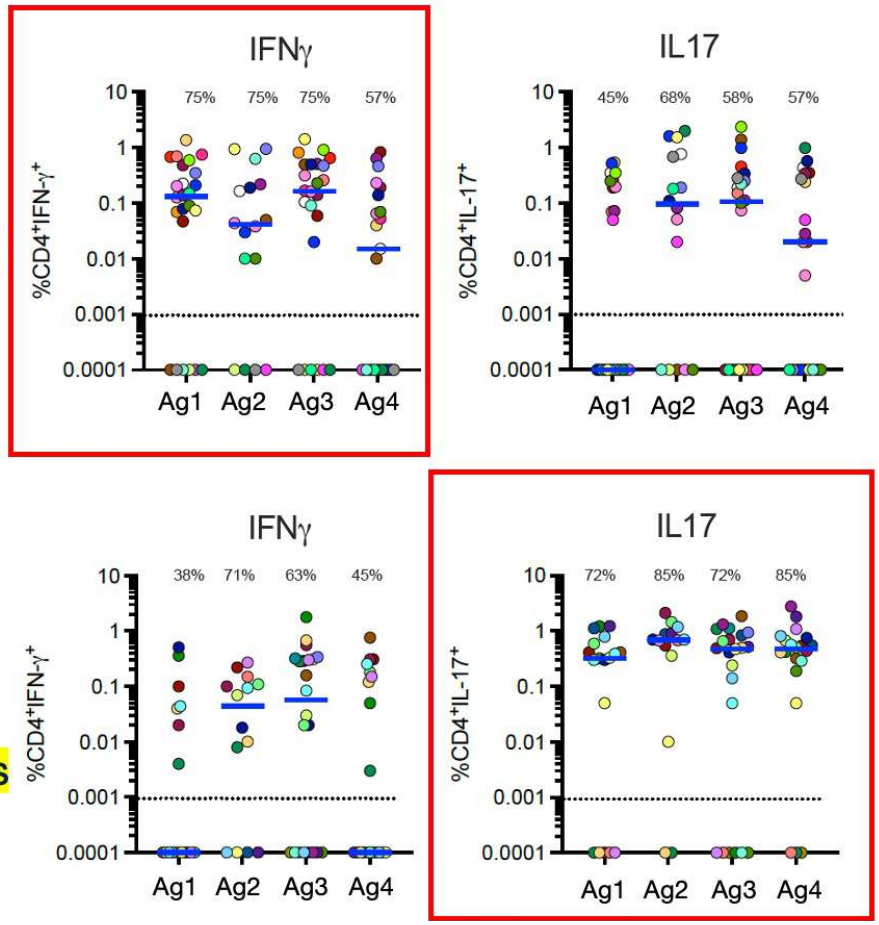
Household contacts (QFT+/HIV-) of confirmed index TB case(smear+ /Xpert med/high)

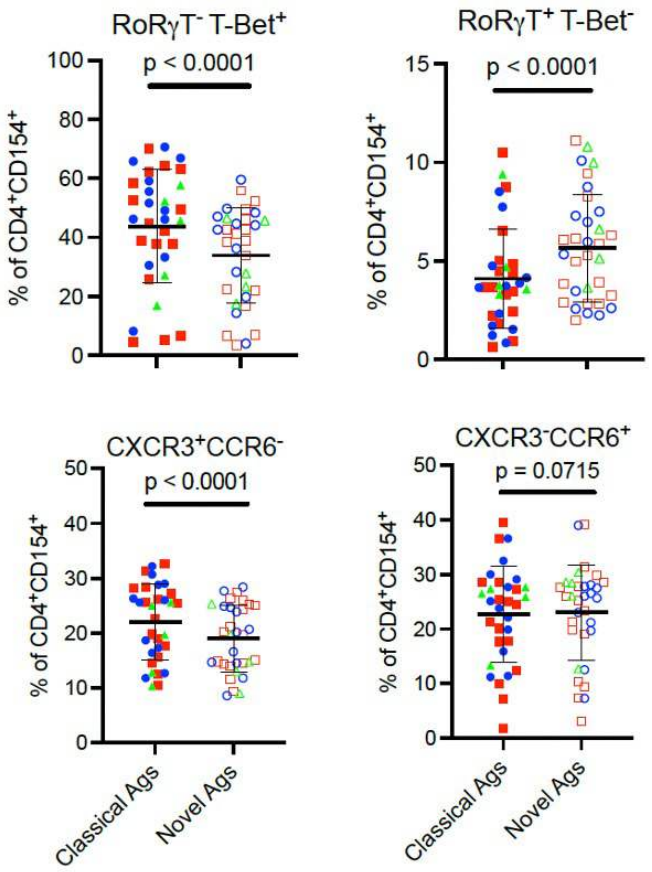
2 sets of distinct *Mtb* antigens: 'conserved' vs 'variable' T cell epitope

Mtb antigens under evolutionary selection skew T cells towards Th17 phenotype

Classical antigens

Novel antigens



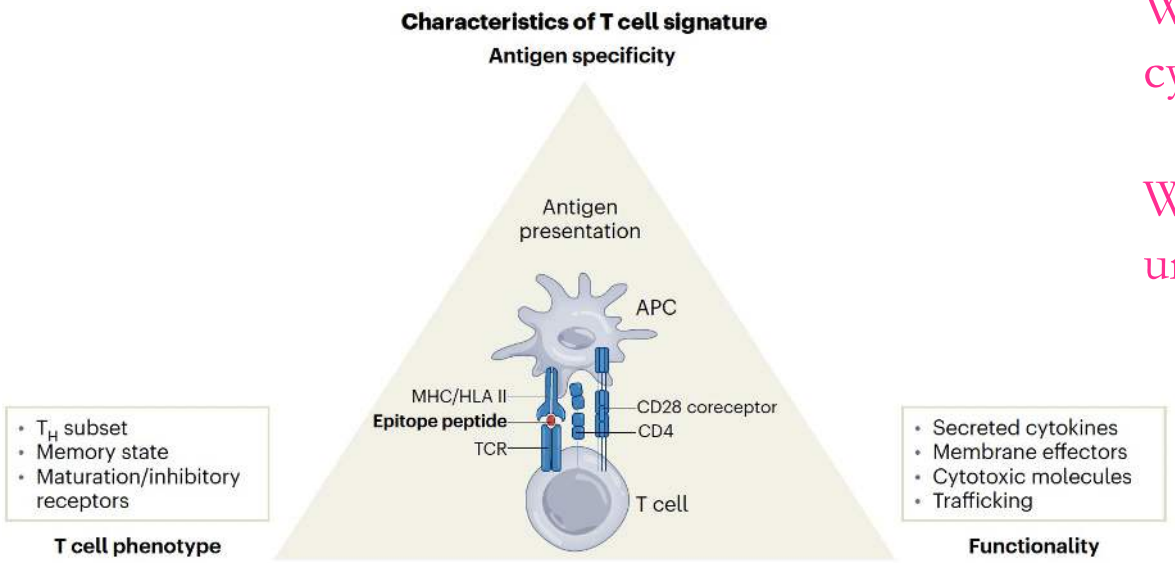


Ogongo, Ernst et al Unpublished

Correlates of protective immunity against TB disease

Need to identify antigens that elicit responses that differentiate progressors from non progressors

What is the right T cell signature?



What is the contribution of cytokine milieux?

What is the role of bystander or uninfected APCs (antigen export)?

Ogongo and Ernst 2023

- **An effective vaccine against TB should elicit a combination of T cell characteristics**

Conclusions and existing gaps

- Distinct *Mtb* antigens are associated with infection outcomes
- Responses to distinct antigens can precede the development of TB disease
- Distinct *Mtb* antigens can determine human T cell differentiation pattern
- Do *Mtb* antigens associated with progression or control induce different immune responses?
- What is the contribution of cytokine milieux in determining *Mtb* antigen-specific T cell responses?
- What is the role of bystander or uninfected APCs (antigen export) in T cell activation?

Acknowledgements

TB Household Contact

- **Joel Ernst, MD**
- Anthony Tran
- Devin Columbus
- TBRU-Astra Clinical core

KEMRI- Kisumu

- Gregory Ouma
- Samuel Gurrion

AHRI - Ethiopia

- Liya Wassie, PhD
- Kidist Bobosha, PhD
- Clinical research team

Ernst Lab

- Jason Limberis, PhD
- Zach Howard
- All members: past and present

Study participants

FUNDING

TBRU | ASTRa
Antigen Specific T-cell Responses and the control of TB

U19 AI 111211